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ARTICLE

Combination of antidepressants and antipsychotics as a novel treatment option for psychosis in Alzheimer's disease

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Abstract

Psychotic symptoms are reported as one of the most common complications of Alzheimer's disease (AD), in whom they are associated with more rapid deterioration and increased mortality. Empiric treatments, namely first and second-generation antipsychotics, confer modest efficacy in patients with AD and with psychosis (AD+P) and themselves increase mortality. Recent studies suggested the use and beneficial effects of antidepressants among patients with AD+P. This motivates our rationale for exploring their potential as a novel combination therapy option among these patients. We included electronic medical records of 10,260 patients with AD in our study. Survival analysis was performed to assess the effects of the combination of antipsychotics and antidepressants on the mortality of these patients. A protein–protein interaction network representing AD+P was built, and network analysis methods were used to quantify the efficacy of these drugs on AD+P. A combined score was developed to measure the potential synergetic effect against AD+P. Our survival analyses showed that the co-administration of antidepressants with antipsychotics have a significant beneficial effect in reducing mortality. Our network analysis showed that the targets of antipsychotics and antidepressants are well-separated, and antipsychotics and antidepressants have similar Signed Jaccard Index (SJI) scores to AD+P. Eight drug pairs, including some popular recommendations like aripiprazole/sertraline, showed higher than average scores which suggest their potential in treating AD+P via strong synergetic effects. Our proposed combinations of antipsychotic and antidepressant therapy showed a strong superiority over current antipsychotics treatment for AD+P. The observed beneficial effects can be further strengthened by optimizing drug-pair selection based on our systems pharmacology analysis.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Current treatments for Alzheimer's disease with psychosis (AD+P) are restricted by their modest efficacy and poor safety profiles. Better treatment options are in urgent need.

WHAT QUESTION DID THIS STUDY ADDRESS?

Will the combination of antipsychotics and antidepressants be a better treatment option? Which antipsychotics and antidepressants are the best pair?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study proved that the combination of antipsychotics and antidepressants showed superiority over antipsychotics monotherapy and proposed several drug pairs that may possess higher efficacy.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

Our results supported the efficacy of antipsychotics and suggested the most promising antidepressants, such as sertraline and maprotiline, can be added as supplementary treatment. In addition, because they are all marketed drugs and some of their combinations are already tested by clinical trials for other indications, the safety profile will not be a major concern when proposing their long-term usage as an alternative treatment option for patients with AD.

INTRODUCTION

Approximately more than 50% of patients with Alzheimer's disease (AD) experience psychotic symptoms and other neuropsychiatric complications.[1] Patients with AD with psychosis (AD+P) are considered a subgroup of patients who experience more severe symptoms, including greater cognitive impairment and a quicker cognitive decline.[2] AD+P is also associated with higher rates of co-occurring agitation,[3] aggression,[3] depression,[4] mortality,[5] functional impairment,[6] and increased caregiver burden than patients with AD without psychosis (AD−P).

Currently, no specific medication has been approved by the US Food and Drug Administration (FDA) for AD+P. Second-generation antipsychotics (SGAs) have been widely used and recommended by geriatric experts in the management of psychosis in AD.[7] However, their usage is greatly limited by increased risk of adverse events and the likelihood of comorbid health problems.[8] This prompted the FDA to issue a "black-box" warning in 2005 to highlight the increased risk of mortality for patients with dementia who are treated with SGAs.[9] Meanwhile, antipsychotics have demonstrated modest efficacy in treating psychosis, aggression, and agitation in individuals with dementia.[10] This emphasizes the need to develop safer and more effective treatment options for AD+P.

Based on our previous studies, antipsychotics do not engage the underlying biology of AD+P, and therefore their modest effectiveness is unsuprising.[11] In order to identify safe and effective treatments for AD+P, it is essential to have a comprehensive understanding of the underlying biology of AD+P. A recent study reported that the heritability of psychosis in AD is estimated to be 61%, thus suggesting a strong association between AD+P and genetic variations.[12] Another study performed a large genomewide meta-analysis on 12,317 patients with AD with or without psychosis.[13] The authors reported that AD+P was not significantly genetically correlated with schizophrenia, but it was negatively correlated with bipolar disorder and positively correlated with depression. These associations provide a biologic rationale for repurposing antidepressant agents as novel treatment options for AD+P in our current study.

To answer if antidepressants are effective in managing neuropsychiatric symptoms in patients with AD, nine clinical trials involving 692 patients were conducted, whereas only two antidepressants, sertraline (Zoloft) and citalopram (Celexa), were studied. Five of nine trials compared antidepressants with placebo and the other four compared with antipsychotics.[14–23] However, only two selective serotonin reuptake inhibitors (SSRIs), which is a subtype of antidepressants, sertraline (Zoloft) and citalopram (Celexa) were studied. As for the antipsychotics, in most studies were typical antipsychotics (haloperidol and perphenazine), whereas only one trial studied an SGA (risperidone). Among the five studies comparing SSRIs with placebo, two of them reported a significant benefit for citalopram against AD+P.[14,16]

Meanwhile, no significant difference was reported between the efficacy of SSRIs and risperidone. Therefore, testing more antidepressants, especially other classes of antidepressants such as serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors, may be worthwhile to provide a better understanding of the impact of antidepressants on AD+P.

Although antipsychotics and antidepressants both have shown beneficial effects against AD+P, they have different targets which in turn can modulate different biological pathways. Thus, the combination of these drugs can potentially provide multiple advantages like enhanced efficacy, decreased dosage with an equal or increased level of efficacy, and delayed development of drug resistance. Due to the excessive time and cost it takes to clinically test the drug combination effects, exhaustive computational methods can be used to predict drug synergy. By integrating information from drugs and diseases we can obtain a comprehensive picture of the potential synergetic effects of these drug combinations. The goal of our study is to further identify key combinations of antipsychotics and antidepressants that possess potential synergetic effects against AD+P with the help of our state-of-the-art quantitative systems pharmacology approaches.

Network approaches have been used in predicting and identifying the disease genes in multiple studies and some of the results have been verified.[24] Protein–protein interaction (PPI) network analysis is a widely used approach to study the functional relationships among proteins and identify potential associations among disease, medications, biological process, etc. PPI network analysis can be used to predict drug actions. PPI networks can provide a systems-level view of how proteins interact with each other and can help identify key nodes in the network that are potential drug targets. One approach to using PPI networks for drug discovery is to identify protein hubs,[25] which are highly connected proteins that play important roles in cellular processes. Targeting these hubs with drugs can potentially have a large impact on the network and lead to therapeutic benefits. Another approach is to identify modules or clusters of proteins that are involved in specific biological pathways or processes.[26] These modules can be used to identify new drug targets or to predict the effects of drugs on the network. The verification of drug effect predicted by a PPI network analysis may involve biological experiments or clinical observations. The experiment can be cell-based or in vivo studies. In addition, if the drug of interest is already on the market, studies on the real-world evidence may also help in validating the predicted results.

MATERIALS AND METHODS

Dataset collection

To explore the beneficial effect of combination therapy, we examined the data from January 2004 to October 2019 from the Neptune system at the University of Pittsburgh Medical Center (UPMC), which manages the use of patients' electronic medical records (EMRs) from the UPMC health system for research purposes (rio.pitt.edu/services). The database includes demographic information, diagnoses, encounters, medication prescriptions, prescription fill history, and laboratory tests. Patients with AD were identified using International Classification of Disease 9th and 10th revisions (ICD-9/10) codes (331.0, G30.0, G30.1, and G30.9) and the onset of psychosis were defined by ICD-9/10 codes (780.1, F06.0, R44.2, R44.1, R44.3, R44.0, 298.8, F22, F23, F28, F29, 293.82, 298.9, 290.11, 293, and 290.3) based on the suggestions from UPMC clinicians. The complete list of antipsychotics and antidepressants that were included in this study is listed in Table S1.

Survival analysis

We included patients who met the following inclusion criteria: (1) the patient had an AD diagnosis; and (2) patients did not take antidepressants nor antipsychotics 1 year prior to the diagnosis of AD. Nine comorbidities, including major depressive disorder (MDD), stroke, chronic obstructive pulmonary disease, atherosclerotic cardiovascular disease, type 2 diabetes, hypertension, chronic kidney disease, heart failure, and cancer, were considered as confounders in our survival analysis. The time origin for each patient in the survival analysis is the first AD diagnosis date and time to all-cause death is the outcome. Patients are marked with the above comorbidities if they were diagnosed before the AD diagnosis. Only medications that are prescribed to the same patients more than two times with more than 30 days apart were considered to eliminate short-term usage during hospitalization. The records of patients up to 5 years after the AD diagnosis were used in the analysis.

Time to all-cause death was constructed as the time between the first date of AD diagnosis and death. Patients who were alive by the end of 5 years since AD diagnosis were censored. Survival analysis was performed to evaluate the association between medications and mortality. To accommodate the change of drug usage during the follow-up, we fitted a time-dependent Cox's proportional hazards model with antipsychotic drug effect (yes or no) and antidepressant drug effect (yes or no) as time-dependent covariates. Specifically, the 5-year follow-up

period was divided into 60 months, and we assumed the drug effect from one prescription will last 2 months, which covers two intervals in our study. As shown in Figure 1, if a patient had an antipsychotics prescription in the first month, we consider the patient under drug effect for that month and the month after. If a patient was prescribed both antipsychotics and antidepressants (boxed in Figure 1), we consider the patient under combinational therapy. The drug effect on one patient may change over time among four statuses: no drug, antipsychotics only, antidepressants only, and the combination. Baseline demographics and comorbidities were also included in the model. Contrasts between different drug groups were performed with hazard ratios and *p* values reported. The data were analyzed using both R (version 4.1.0) and Python (version 3.7.12) packages.

Prediction of synergetic effect among antipsychotic-antidepressant pairs

Because the analyses conducted are a mixed effect of any combination of antipsychotics and antidepressants, we further examined if certain antipsychotic-antidepressant pairs may possess higher synergetic effect in managing psychotic symptoms in AD. We first attempted this evaluation by using EMR data. However, because of the large number of antipsychotics and antidepressants used clinically, the appearances of specific drug pairs are limited (most co-administrated pair: Quetiapine and Sertraline, 408 times; more data are in Table S2), and their overlap times are too short to produce enough statistical power. Therefore, we turned to systems pharmacology approaches to identify antipsychotic-antidepressant pairs that are most suited in treating AD+P.

Given that synapse loss is the main neuropathologic indicator of cognitive decline in AD, it has been postulated that the susceptibility to AD+P results from more synaptic impairment in AD+P compared to AD–P.[27] A recent study reported that patients with AD+P had reduced postsynaptic density (PSD) proteins compared to patients with AD–P, so we used the only proteome data for AD+P in this study for more accurate results.[28] The PSD proteome was used to build the AD+P network. This proteomic signature was generated by Dr. Sweet's team.[27] Information about antipsychotics, antidepressants, and their targets were extracted from DrugBank (https://www.drugbank.ca/).[29] The pharmacological action label of a drug provides information about whether binding to a target contributes to the pharmacological effects. PPI data were collected from STRING (https://string-db.org/).[30] The PPI networks were constructed and analyzed using the Python package networkx (https://networkx.github.io/). The interaction network was shown in the molecular action view with medium confidence level (>0.4).[31] AD+P-related proteins were joined with targets of antipsychotics and antidepressants to construct the disease-target network. In addition, we also included the proteins bridging proteins from disease module and proteins from the target module in our disease-targets networks. Gene signature data were used to calculate the proximity for drugs and AD+P. The post-treatment gene signature data were obtained from the LINCS L1000 database.[32]

There are several characteristics in the network analysis area that were used to quantify the topology position of a node in a network including degree, betweenness, average path length, and modularity.[33] In addition, other approaches like the Triadic Closure Principle and paths of length 3 (L3) were also studied to predict potential interactions between protein targets.[34] Because the main focus of this study is to evaluate the difference of drug effect in AD+P, nodal efficiency, which is the measurement for efficient network structures, were used in this study.[35]

FIGURE 1 Schematic diagram for identifying drug usage status of subjects. In the upper two rows of Figure 1, the sections with 1 indicate that there are antipsychotics/antidepressants prescriptions in that month, whereas 0 means there are no prescriptions for the two kinds of medications. In the lower rows, the sections under 1 are extended for 1 month to reflect the drug effect, thus these markers show the time that the subject was under the drug effect.

To predict potential drug combinations for AD+P, we adopted the methods from Chen et al.[36] and modified them by incorporating differentially expressed genes after drug treatment to minimize the bias caused by module sizes. Based on previous studies, for a drug pair to have a therapeutic effect on a disease, both target modules (green and yellow circles in Figure 2) of the two drugs must overlap with the disease module (pink circle in Figure 2).[36] In addition, the two target modules need to be overlapped with the disease module independently to form a complementary exposure to have synergetic effects with each other, as shown in Figure 2. To be specific, the targets of the two drugs both need to be overlapped with the disease module in the PPI network, but these two target modules cannot overlap.[36] Therefore, two network approaches are applied to predict the possible drug combinations for AD+P: (1) network-based separation between targets of two drugs; (2) gene signature-based SJI score between the disease (AD+P) module and the target modules of the two drugs.

Separation evaluation

The separation score (S_{AB}) of drug modules A and B are calculated for all possible combinations between antipsychotics and antidepressants. The separation score (S_{AB}) of drug modules A and B can be calculated as:

$$S_{AB} = <d_{AB}> - \frac{<d_{AA}> + <d_{BB}>}{2} \quad (1)$$

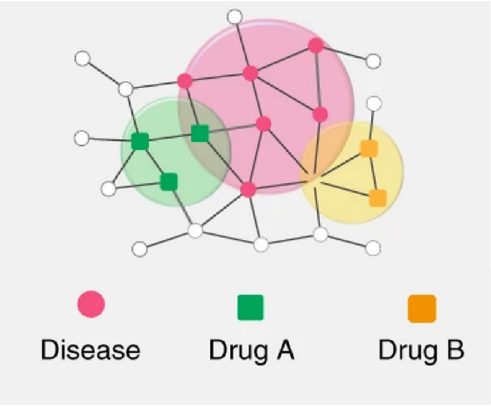

FIGURE 2 Schematic diagram for the network-based complementary exposure relationship between two drug–target modules and one disease module on a drug–drug–disease combination (adopted from Guney, E.; Menche, J.; Vidal, M.; Barábasi, A.-L., Network-based in silico drug efficacy screening. Nature communications 2016, 7 (1), 1–13.[37]). Big red circle: AD+P modules composed of AD+P related proteins/genes (small red rounds). Green and yellow circle: Drug modules composed of drug targets. AD+P, Alzheimer's disease with psychosis.

where $<d_{AA}>$, $<d_{BB}>$, and $<d_{AB}>$, are the mean shortest distance for genes within each module. It compares the mean shortest distance between the targets of each drug. For better understanding, if $S_{AB} < 0$, it means that the targets in the two drug modules are in the same network neighborhood which is not separated; if $S_{AB} \geq 0$, it means that the two drug modules are topologically separated from each other. We filter the combinations based on their ability to achieve complementary exposure with the AD+P module.

Proximity evaluation

Level 5 LINCS L1000 data, a collection of gene expression profiles for thousands of perturbagens at a variety of timepoints, doses, and cell lines, were downloaded from the GEO database (accession numbers: GSE70138 and GSE92742). Gene expression profiles were included only if they are tested on a cell line of central nervous systems and their dose should be beyond 1 uM. To identify genes that are significantly differentially expressed in the data, their Z scores from multiple tests were averaged and if their $|Z| > 1$, the genes are considered as significant for a drug.[38]

The association between the drug and AD+P was quantitatively evaluated with the SJI score, which is defined in our previous study.[39] The index ranges from +1 to −1, where +1 and −1 indicate a same pattern and an inverse pattern of two identical gene sets, respectively. Zero indicates that the two sets have no overlap, or the positive and negative correlations cancel out.

RESULTS

After applying all inclusion criteria to our dataset, 10,206 unique patients with AD were identified and 9578 of them met the inclusion criteria. Their baseline characteristics are shown in Table S3. For the four different groups out of the total 10,206 patients with AD, 7305 of them have no antipsychotics or antidepressants. Three hundred ninety-one of them had antipsychotics only, 1470 of them had antidepressants only, and 412 of them had the combination of antipsychotics and antidepressants.

Use of antipsychotics in patients with AD is associated with increased mortality

Prior literature has reported that the use of antipsychotics is associated with increased mortality in patients with AD [40]; we therefore first sought to replicate this finding to validate the integrity of our methodological approach. The

TABLE 1 Multivariate Cox regression analyses of association between antipsychotics and all-cause mortality in patients with AD.

Covariate	Hazard ratio	Hazard ratio lower 95%	Hazard ratio upper 95%	*p* value
Antipsychotics vs. no antipsychotics	2.47	1.978	3.084	<0.001
Age	1.051	1.047	1.055	<0.001
Gender (female vs. male)	0.712	0.676	0.751	<0.001
Race (other vs. White)	1.622	1.427	1.841	<0.001
Race (Black vs. White)	0.698	0.636	0.767	<0.001
ASCVD	1.136	1.06	1.216	<0.001
CKD	1.304	1.226	1.386	<0.001
COPD	1.175	1.107	1.247	<0.001
Cancer	1.088	1.023	1.157	0.007
HF	1.411	1.33	1.498	<0.001
HTN	1.004	0.934	1.079	0.906
MDD	1.154	1.092	1.22	<0.001
Psychosis	1.192	1.101	1.29	<0.001
Stroke	0.938	0.869	1.011	0.095
T2DM	1.131	1.07	1.195	<0.001
AD Medication	0.907	0.858	0.959	0.001

Abbreviations: AD, Alzheimer's disease; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; HTN, hypertension; MDD, major depressive disorder; T2DM, type 2 diabetes.

time varying Cox model was conducted with our data to test the significance.

As indicated in Table 1, antipsychotic usage is significantly associated with increased mortality in patients with AD (hazard ratio [HR] = 2.47, $p < 0.001$). The results showed in this table are in accordance with current literature, which suggest that our data and methods are valid for further analysis.[9]

Survival analysis revealed significant beneficial effect combining antidepressants and antipsychotics in patients with AD

After knowing that antipsychotics may increase mortality in patients with AD, whereas antidepressants may decrease mortality, the effect of a combination therapy comes into play. We would like to examine the protective effects of adding antidepressants to the existing antipsychotics therapy. We performed another survival analysis to examine three mutually exclusive medication use groups: antipsychotics only, antidepressants only, and combination.

The results are shown in Table 2 and the combination group is the reference group in this model. Based on the results from Table 2, the combination group showed a significant beneficial effect relative to antipsychotics only group (HR = 0.654, $p = 0.012$), which means that combining antidepressants with antipsychotic treatment was associated with significantly protective effects in patients with AD, reducing mortality. In addition, marginal significant difference was observed between the no drug group and the combination group (HR = 1.294, $p = 0.056$), which means that by using combination therapy, the increase in mortality due to using antipsychotics was mitigated to some extent in these patients.

Based on our findings shown in Tables 1 and 2, we can conclude that by combining antipsychotics and antidepressants, we can significantly mitigate the increase in mortality associated with antipsychotics. For more direct comparison between different treatment groups, a table with pair-wise comparison among groups is included in Table S4.

In addition to these results, we were interested to see if the effect of the treatments will change over time. Therefore, we conducted six analyses with follow-up times ranging from 1 to 6 years. We compared the effects of three different treatments (antipsychotics only, antidepressants only, and no drug) to the drug combination group, their effects showed moderate fluctuation within the first 3 years and stabilized after 4 years (Figure S1). In comparison to co-administration of antidepressants and antipsychotics, the antidepressants only group showed

TABLE 2 Multivariate Cox regression analyses of association among treatments and all-cause mortality in patients with AD.

Covariate	Hazard ratio	Hazard ratio lower 95%	Hazard ratio upper 95%	*p* value
Antidepressants only vs. drug combination	0.518	0.382	0.703	<0.001
Antipsychotics only vs. drug combination	1.528	1.099	2.123	0.012
No drug vs. drug combination	1.294	0.993	1.684	0.056
Age	1.051	1.047	1.055	<0.001
Gender (female vs. male)	0.712	0.676	0.751	<0.001
Race (Other vs. White)	1.622	1.427	1.841	<0.001
Race (Black vs. White)	0.698	0.635	0.766	<0.001
ASCVD	1.135	1.059	1.215	<0.001
CKD	1.304	1.226	1.386	<0.001
COPD	1.175	1.107	1.247	<0.001
Cancer	1.088	1.023	1.158	0.007
HF	1.411	1.33	1.497	<0.001
HTN	1.004	0.935	1.08	0.905
MDD	1.156	1.094	1.222	<0.001
Psychosis	1.193	1.102	1.292	<0.001
Stroke	0.938	0.87	1.012	0.097
T2DM	1.131	1.07	1.195	<0.001
AD Medication	0.906	0.857	0.958	0.001

Abbreviations: AD, Alzheimer's disease; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; HTN, hypertension; MDD, major depressive disorder; T2DM, type 2 diabetes.

a consistent lower mortality throughout the 6 years. Whereas the antipsychotics only group had marginally increased mortality compared to the combination group at the first 3 years, subsequent worse outcomes were clearly evident in 4, 5, and 6 years of follow-up. Finally, the combination group showed comparable effects with the patients with no drug treatment throughout the 6 years period and demonstrated almost significant beneficial effects in 4, 5, and 6 years of the follow-up. Our results are attached in Table S5.

Systems pharmacology studies provided possible explanations for the synergetic effects and proposed drug pairs may achieve optimized efficacy

In total, 21 antipsychotics and 17 antidepressants commonly used in the clinic are included in our study along with 75 targets for antipsychotics and 32 targets for antidepressants. The PPI network was built with 240 AD+P proteins, targets for antipsychotics, and antipsychotics. A PPI network with 321 nodes and 1363 edges was generated. A total of 357 pairs of antipsychotics and antidepressants are evaluated in the network and their separation scores are calculated as shown in Figure S2.

We found that some antidepressants showed great separation (Vortioxetine, Vilazodone, Mirtazapine, and Maprotiline), and most drugs pairs showed a separation score above zero (blue). This suggests an existing difference in the mechanism which can be the key condition to the synergetic effect in the combinational therapy.

To evaluate the proximity between AD+P and medications, 148 and 78 eligible expression profiles for antipsychotics and antidepressants were collected based on the inclusion criteria described earlier. The SJI scores were calculated between them and AD+P protein expressions.

Post-treatment gene expression data for 16 antipsychotics and 13 antidepressants were exacted, and their SJI scores were calculated accordingly and are shown in the tables below.

To comprehensively evaluate the potential for these drug combinations, separation scores and SJI scores were normalized to a [−1, 1] interval and combined. A combined score was calculated for every drug pair by subtracting two SJI scores of the drugs from their separation score. The combined scores for drug pairs are shown in the heatmap below (Figure 3).

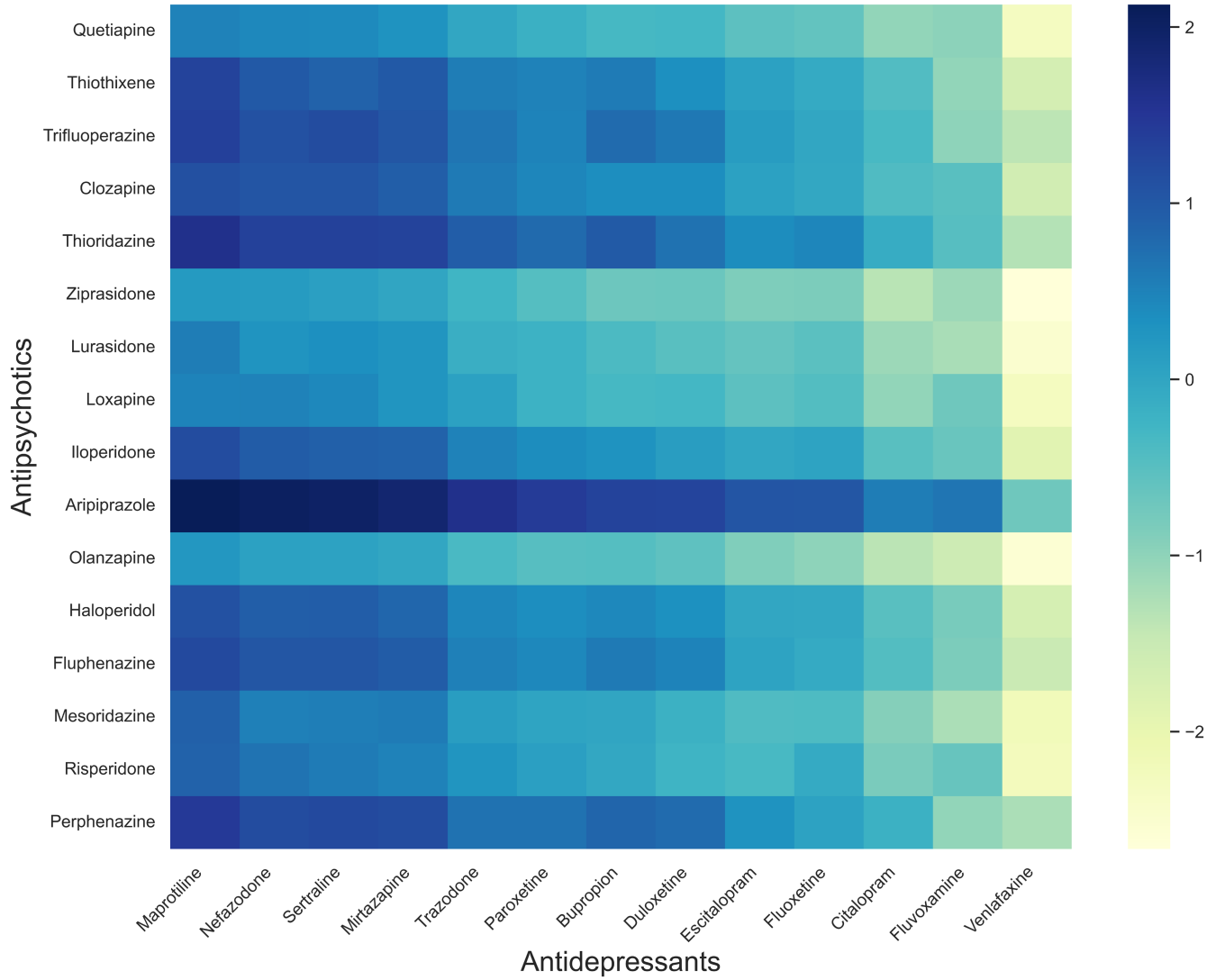

FIGURE 3 Combined scores for antipsychotics and antidepressants combinations. Although most drug pairs showed a combined score around 0, some drugs do show promising scores across the board, including Aripiprazole and Thioridazine.

As shown in Figure 3, most drug pairs showed a combined score around zero, which indicate that the synergistic effect between antipsychotics and antidepressants may not be easily achieved within the two drug categories. However, some drugs showed promising results through the panel, like Aripiprazole and Thioridazine. For drug combinations that may possess beneficial synergistic effect, they must meet the following criteria: (1) the separation score between two drugs greater than 0; and (2) the SJI scores of the two drugs less than 0.

Among the nominated drug combinations, Aripiprazole is the only SGA and is also the most recommended treatment options for AD+P. As a matter of fact, the combination of Aripiprazole and Sertraline has already been tested in clinical trials and showed superior efficacy in treating MDDs with no reports of safety concerns.[41] However, none of these drug pairs have been tested for AD+P in clinical trials. As a matter of fact, no combination drug therapy has ever been tested for AD+P at present.

DISCUSSION AND CONCLUSION

In this study, we applied a combination of different state-of-the-art systems pharmacology techniques to explore the potential synergetic effect of combining antipsychotics and antidepressants in treating AD+P. This study incorporated different data types, including clinical EMR data, protein expressions, post-treatment gene expressions, and PPI networks. Our results indicate that the combination of antipsychotics and antidepressants may be a safer and more efficient treatment option for AD+P and provided informative insights for drug pairing choices for future therapies.

The two sections of this study proved the superiority of the combination therapy over antipsychotics mono therapy

TABLE 3 Signed Jaccard Index scores of antipsychotics and antidepressants with AD+P.

Antipsychotics	Drug perturbed genes	Overlap	Same	Inverse	SJI score
Aripiprazole	3384	71	9	59	−0.01028
Thioridazine	7670	135	47	78	−0.00573
Clozapine	3801	57	13	38	−0.00334
Iloperidone	4868	78	31	39	−0.00285
Thiothixene	2109	39	23	16	−0.00247
Trifluoperazine	6286	96	21	57	−0.0024
Haloperidol	1083	22	9	12	−0.00216
Risperidone	1460	15	5	9	−0.00199
Fluphenazine	1180	20	9	11	−0.0019
Perphenazine	4758	87	23	64	−0.00176
Lurasidone	1480	17	6	9	−0.00034
Quetiapine	831	6	3	3	0.000232
Loxapine	2488	34	18	14	0.000386
Mesoridazine	2334	28	10	18	0.000986
Ziprasidone	3995	65	28	33	0.001916
Olanzapine	1013	15	11	4	0.002919
Antidepressants					
Duloxetine	4710	81	17	58	−0.00851
Sertraline	5696	104	19	83	−0.00806
Maprotiline	1271	25	8	17	−0.00676
Nefazodone	1393	34	13	21	−0.00645
Mirtazapine	3105	56	26	30	−0.00488
Bupropion	600	14	5	9	−0.00455
Trazodone	3002	49	31	18	−0.00335
Paroxetine	5379	103	34	69	−0.00202
Fluoxetine	2776	47	18	24	−0.0003
Escitalopram	1977	30	14	16	0.000369
Fluvoxamine	4572	79	31	38	0.000892
Citalopram	2083	30	10	19	0.003719
Venlafaxine	1023	11	10	1	0.005222

Abbreviations: AD+P, Alzheimer's disease with psychosis; SJI, Signed Jaccard Index.

from different aspects. Therefore, these two sections can serve as cross validations at some extent. It is without doubt that more studies need to be conducted to further validate the beneficial effect of antidepressants in AD+P. For example, due to the limitation of sample size, we were not able to acquire decent groups for specific drug combinations in the EMR data and it will be of great value if we can expand our research to include more patients to verify the specific drug pairs that have been proposed by the mechanism study.

When dealing with real-world data, like EMRs, there is always a challenge that the compliance of patients presented in the EMR will not be as ideal as we get from a carefully performed clinical trial. In this study, by analyzing real-world EMR data through the Cox model with time-dependent covariates, we were able to accommodate the complex usage patterns and allowed the maximum utilization of the data. The beneficial effect of antidepressants in patients with AD were reported by multiple studies,[42,43] although its mechanisms remain unclear. We also found a strong signal in our results (Table 3 and Figure 3) which further substantiated our claim that antidepressants may aid in reducing mortality in patients with AD. Our finding provided the fundamental support necessary for our hypothesis that by combining antipsychotics and antidepressants, we can decrease the severe side effect that is constraining the use of antipsychotics in AD therapy.

In order to provide mechanistic support for our observations and identify the most potent drug combinations

TABLE 4 Antidepressants and antipsychotics combinations with highest combined scores.

Antipsychotics	Antidepressants	Antipsychotics SJI score	Antidepressants SJI score	Separation score	Combined score
Aripiprazole	Maprotiline	−1	−0.745	0.382	2.13
Aripiprazole	Nefazodone	−1	−0.7	0.345	2.05
Aripiprazole	Sertraline	−1	−0.934	0.0545	1.99
Aripiprazole	Mirtazapine	−1	−0.472	0.418	1.89
Thioridazine	Maprotiline	−0.311	−0.745	0.564	1.62
Aripiprazole	Trazodone	−1	−0.248	0.364	1.62
Aripiprazole	Paroxetine	−1	−0.0542	0.364	1.42
Thioridazine	Nefazodone	−0.311	−0.7	0.3277	1.34
Thioridazine	Sertraline	−0.311	−0.934	0.0909	1.34
Thioridazine	Mirtazapine	−0.311	−0.472	0.527	1.31
Thioridazine	Bupropion	−0.311	−0.423	0.236	0.971
Thioridazine	Trazodone	−0.311	−0.248	0.382	0.941
Thioridazine	Paroxetine	−0.311	−0.0542	0.418	0.783

Abbreviation: SJI, Signed Jaccard Index.

for treating AD+P, we took advantage of multiple categories of data, including PPI network, post-treatment gene expression profiles to quantitatively evaluate the potential synergistic effect of antipsychotics and antidepressants. Our analysis yielded several pairs of drugs that may possess better synergistic effects in treating AD+P. As shown in Table 4, two antipsychotics: Aripiprazole, Thioridazine, were reported, and seven antidepressants: Sertraline, Maprotiline, Nefazodone, Mirtazapine, Trazodone, Paroxetine, and Bupropion were mentioned. Between the two antipsychotics, Thioridazine is a first-generation antipsychotic and it was withdrawn worldwide in 2005 due to its association with cardiac arrythmias.[44] For Aripiprazole, it has been reported with significant better efficacy in patients with AD against psychological symptoms[45] which further consolidate our conclusions. For the seven antidepressants, Nefazodone was discontinued in 2004 because of its association with drug-induced hepatic injuries.[46] For the rest of the six antidepressants, they belong to four classes. Sertraline, Trazodone, Paroxetine are SSRIs, which is the most used antidepressant class.[47] Maprotiline is a tetracyclic antidepressant with similar pharmacological properties to tricyclic antidepressants, it can inhibit neuronal norepinephrine reuptake, possesses some anticholinergic activity, and does not affect monoamine oxidase activity.[48] Mirtazapine is a tetracyclic *piperazinoazepine* antidepressant, which its effect can be observed as early as 1 week after beginning therapy,[49] it has also been reported to be efficacious in the off-label management of various other conditions. It may improve the symptoms of neurological disorders, reverse weight loss caused by medical conditions, improve sleep, and prevent nausea and vomiting after surgery.[50] Bupropion is a norepinephrine/dopamine-reuptake inhibitor antidepressant, and it is a unique option for the treatment of MDD as it lacks any clinically relevant serotonergic effects, typical of other mood medications, or any effects on histamine or adrenaline receptors.[51]

As for combination therapy consisting of antipsychotics and antidepressants, although they were never tested specifically for AD or AD+P, multiple studies have tested their safety and efficacy profile against other disorders. For example, a meta-analysis consisting of eight randomized, placebo-controlled studies reported that antidepressant-antipsychotic co-treatment was superior to monotherapy with either drug class in the acute treatment of psychotic depression[52] and another study reported that adding SGAs to antidepressants yielded highly significant superiority in treating MDD as well.[53] In that study, Aripiprazole, Olanzapine, Risperidone, and Ziprasidone were found to be more effective than other SGAs.[53]

Our study has a few limitations. For the EMR analysis, due to the limitation of sample size, we were not able to specify the effect of different drug combinations or even different subclasses of drugs. It will be of great value if we can expand our research to include more patients and examine the beneficial effect of specific drug pairs. As the present study is based on retrospective observational data obtained from EMRs, it is important to acknowledge that there may exist additional factors that are associated with both antidepressant and/or antipsychotic usage and mortality among patients with AD+P, which were not included in our analysis due to the limitations of the EMR data. Among such factors are various social

determinants of health, including educational attainment, wealth, access to health care, degree of social interaction and strength of social networks, functional limitations, and malnutrition, among others, which have been shown to potentially impact the progression of AD+P.[54] The direction and magnitude of these unmeasured confounders may also provide valuable insight into the development of AD+P. Future studies with a larger data size and better coverage of data or even clinical trials can be conducted to validate the findings of our study. In addition, the PPI network we built is restricted by the existing studies related to the proteins within our dataset, it will be biased by the amount and the quality of the studies.

In the two sections of this study, the first section presented that the combination of antipsychotics and antidepressants showed superior safety profile in patients with AD. We reported that the addition of antidepressants has nearly eliminated the increased mortality rate by the use of antipsychotics. The second section provided molecular mechanism supports for the potential synergetic effect for the combination of antipsychotics and antidepressants in patients with AD+P. The combination of the results of the two sections provided evidence for the superiority of combination therapy from both efficacy aspect and safety aspect. Our results supported the efficacy of antipsychotics and suggested the most promising antidepressants, such as Sertraline and Maprotiline, can be added as supplementary treatment. In addition, because they are all marketed drugs and some of their combinations are already tested by clinical trials for other indications, safety profile will not be a major concern when proposing their long-term usage as an alternative treatment option for patients with AD.

AUTHOR CONTRIBUTIONS

P.F., L.Z., L.W., J. Kofler, J.S., and J. Krivinko wrote the manuscript. P.F., L.W., R.A.S., and Y.D. designed the research. P.F. and L.Z. performed the research. P.F. and L.Z. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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